Recombinant human erythropoietin counteracts cisplatin-induced visceral hyperalgesia

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Abstract: Objective Cisplatin exerts its cytotoxic effect through distinct DNA lesions, leading to peripheral neuropathy. The risk of sensory neuropathy is a common problem during cancer treatment with cisplatin, leading to somatic hyperalgesia. Yet, data focussing on cisplatin-induced impairment of the autonomic nervous system are limited. The present study was aimed to investigate the effect of recombinant human erythropoietin (rhEPO) on cisplatin-induced visceral hyperalgesia. **Methods** C57BL/6 mice were treated either with cisplatin (2 mg/kg, once per week) or with cisplatin (2 mg/kg, once per week) plus rhEPO (40 µg/kg, 3 times per week) for 8 weeks. Controls were treated with saline. To quantify the visceromotor response (VMR) at week 9, standardized electrodes were implanted into the external oblique musculature for electromyographic recordings. After that, animals were decapitated and dorsal root ganglia (DRG) was removed for transmission electron microscopy studies. **Results** Cisplatin-treated mice showed a significant increase of VMR compared to the controls [(7080 ± 969) vs (2864 ± 279); $P < 0.001$], while rhEPO dramatically counteracted this effect [(2962 ± 336) vs (7080 ± 969); $P < 0.001$]. Transmission electron microscopy revealed cisplatin-induced structural lesions of nuclear membrane in DRG cells, which could be ameliorated by rhEPO. **Conclusion** Erythropoietin can significantly ameliorate the cisplatin-induced visceral hyperplasia and DRG nuclear membrane structure damage in mice, indicating a neuroprotective role of erythropoietin.

Keywords: cisplatin; dorsal root ganglia; erythropoietin; visceral neuropathy

1 Introduction

Cisplatin is widely used in the treatment of solid tumors. However, its high efficacy in cancer treatment is usually accompanied with severe neurotoxic side effects, affecting the

peripheral nervous system. The sensory neuropathy is a common problem that often leads to therapy withdrawal. The paradoxical combination of sensory loss and reduction in nociceptive threshold results in a painful somatic hypersensitivity. Although an animal model of nociceptive peripheral neuropathy has been introduced^[1], data concerning cisplatin-dependent impairment of the autonomic nervous system and the strategies to circumvent the visceral neuropathy are scarce and mostly focussed on inhibiting sero-

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tonergic pathways^[2]. There is growing evidence that cation channels are involved in the process of neuropathic pain due to cisplatin^[3,4].

The precise mechanisms of cisplatin-induced neurotoxicity remain still unclear. Cisplatin exerts its cytotoxic effect through the interaction with cellular DNA and the formation of distinct platinum (Pt)-DNA adducts^[5]. Accumulation and persistence of DNA adducts in the cell nucleus can lead to cell apoptosis^[6,7]. There is growing evidence that nuclei of DRG neurons are the primary targets of cisplatin-induced neurotoxicity^[8,9]. Recently, we have found that repeated exposure to cisplatin can lead to sensory neuropathy in wild type (DNA repair proficient) mice and more severely in knock-out [xeroderma pigmentosum complementation group A deficient (XPA^{-/-}), xeroderma pigmentosum complementation group C deficient (XPC^{-/-}), DNA repair deficient] mice^[10]. However, neurons in the spinal cord are protected by the intact blood-brain barrier, resulting in an approximately 40% decrease in Pt-DNA adducts^[10].

Moreover, accumulating evidence has indicated that recombinant human erythropoietin (rhEPO) possesses neuroprotective properties^[11,12]. In the peripheral nervous system, erythropoietin and its receptor are expressed in DRG neurons, axons and Schwann cells^[13]. More recently, rhEPO has been demonstrated to produce neuroprotective effect against cisplatin-induced neurotoxicity, without affecting Pt-DNA adduct accumulation in DRG neurons^[14].

Cisplatin-induced significant impairment of sensory nerve function is associated with structural damage in somatic nerves and mitochondria. Administration of rhEPO can rescue the nerves from damage, consequently leading to significant improvement in electrophysiological parameters and a tendency toward improvement of the withdrawal threshold. Besides, rhEPO does not have any effect on the nerve conduction velocity when administered alone^[14].

Based on our previous study on large myelinated somatic fibers, the present study was aimed to extend the understanding of the neuroprotective effects of erythropoietin against cisplatin-induced visceral hyperalgesia. The mouse model of cisplatin-induced visceral hyperalgesia was employed to assess the visceromotor response (VMR) and neu-

ronal cell structural changes in DRG neurons *in vivo*. Since cisplatin causes a systemic side effect, here thoracolumbar DRGs, instead of visceral nerve fibers, were examined.

2 Materials and methods

2.1 Animals and study design

2.1.1 Animals Male C57BL/6/J mice from the Institute of Cell Biology were used throughout the experiment. Mice were housed under specific pathogen free (SPF) conditions with access to 1314 fortified standard diet (Altromin, Germany) and water *ad libitum*, under a 12:12 h dark/light cycle. Mice were aged 20 weeks at the time of behavioral testing. All experiments were approved by the state animal welfare board (G-033/05Z).

2.1.2 Study design Mice were randomly divided into 3 groups (groups A-C), and the number of animals was 17 in group A, 32 in group B and 21 in group C, respectively. Differences in group size were related to an overall animal dropout rate of approximately 15%, due to the drug intolerance, anaesthesiological and surgical complications, or electromyographic (EMG) electrode dislocation. All mice were treated for 8 weeks and were 20 weeks old at the time of examination. Mice in group A were treated with cisplatin (2 mg/kg body weight, i. p., Platinex®, Bristol, Munich, Germany) once per week. To prevent renal damage, the mice were injected with 500 µL saline i.p. after each cisplatin injection. Mice in group B were treated with cisplatin (2 mg/kg body weight, i.p.) once per week and additionally with rhEPO (40 µg/kg body weight, s. c., Neorecormon®, Roche, Basel, Switzerland) 3 times per week. These mice were injected with 500 µL saline i.p. as well to prevent renal damage. In group C, mice were only treated with saline (500 µL, i.p.) once per week as a control. In week 9, colorectal distension was conducted in all the groups. After that, mice were sacrificed and DRGs were removed from thoracic and lumbar regions for histological analysis. Since erythropoietin administration does not affect the peripheral nervous system^[15,16], a fourth group was abdicated to minimize the number of experimental animals.

2.2 Assessment of VMR to colorectal distension

2.2.1 Surgical preparation Under ketamine hydrochloride (1 mL/kg body weight, i.p., Ketamin 10%; Sanofi-Ceva,

Düsseldorf, Germany) and xylazine hydrochloride (0.01 mL, i.p., Xylazin 2%; Sanofi-Ceva, Düsseldorf, Germany) anesthesia, bipolar electrodes (Teflon-coated stainless steel wire; CoonerWire Sales, Chatsworth, Calif., USA) were stitched into the external oblique musculature, just superior to the inguinal ligament, for EMG recording. EMG electrodes were externalized at the dorsal neck of the animals for future access analogous to previous studies on visceral nociception. After surgery, the mice were allowed to recover for 3 d before experimental use.

2.2.2 Distension protocol As visceral stimuli, mechanical distension of the descending colon and rectum was performed by pressure-controlled air inflation of a 0.5-cm flexible plastic balloon connected to an electronic distension device (Distender Series II barostat; G&J Electronics, Willowdale, Ontario, Canada). The balloon was lubricated (Vaseline, general pharmacy of the University of Essen, Germany), inserted intra-anally and positioned 0.75 cm proximal to the anus. Thereafter, the balloon was secured by taping the catheter to the tail. After 180-s baseline stimulation (deflated balloon), a tonic distension with a pressure of 60 mmHg was applied for 180 s, followed by another 180 s of EMG recording with deflated balloon (Fig. 1). This procedure was performed once in each animal. The applied distension protocol had been established in previous studies^[17] and validated via ramp distension protocols. The EMG signal was amplified with the

ISOLAB system (ISOLAB/IDAA, Intestinal Data Acquisition and Analysis; Standard Instruments, Karlsruhe, Germany) by the factor 100 000 and filtered with a band-pass filter with a high selectivity at a centre frequency of 120 Hz. An integrated EMG response was used as the response parameter and VMR was calculated as the area under the curve (AUC) using the ISOLAB software.

2.3 Electron microscopic examination of DRG neurons

DRGs were removed after colorectal distension and fixed in 2.5% glutaraldehyde in phosphate buffer immediately. After being washed by phosphate buffer, tissue samples were osmicated for 1 h with 1% OsO₄ in phosphate buffer, dehydrated in a graded series of alcohol, and embedded in Epon 812 (Shell Chemical of Houston, Texas, USA). Electron microscopic examination was performed using a Zeiss EM 902 transmission electron microscope. DRGs of thoracic and lumbar segments from 5 mice in each group (overall 10 ganglions; 2 ganglia per mouse) were screened. For each group, a total of 400 neurons (40 neurons × 2 ganglia × 5 mice) were examined. Large- and small-sized neurons were considered. All sections were blinded, i.e., the examiner had no knowledge of whether the sections for evaluation were from control or tested group.

2.4 Statistical analysis Data were presented as mean±SEM. The differences of VMR between groups were evaluated by analysis of variance (ANOVA) with Bonferroni correction to control for type I error. All *P* values calculated were two-tailed. *P* < 0.05 was considered as statistically significant. All further (exploratory) analyses were considered significant at an α -level of 5%. All statistical analyses were made using the SPSS software package (version 12.0.1, Chicago, Illinois, USA).

3 Results

3.1 Effect of rhEPO on cisplatin-altered visceral nociception

As shown in Fig. 2, cisplatin treatment enhanced the VMR in response to increased colorectal distension, compared with the control [(7080 ± 969) vs (2864 ± 279); *P* < 0.001], while concomitant application of rhEPO (40 µg/kg, 3 times per week) significantly attenuated this effect [(2962 ± 336) vs (7080 ± 969), *P* < 0.001], indicating that the visceral nociception could

Fig. 1 Original recording of VMR. The upper trace shows the EMG activity, the lower trace shows the colorectal distension. Cisplatin treatment led to an increase in EMG response (B), and the EMG activity did not reach the base level during the tonic phase. EMG activity in controls (A) showed a minor increase.

Fig. 2 Effect of rhEPO on cisplatin-induced visceral neuropathy. Cisplatin treatment significantly enhanced the VMR ($n=17$) compared with the control ($n=21$), while coadministration of rhEPO ($n=32$) abolished these effects completely.

be rescued by rhEPO.

3.2 Histopathological findings The neurotoxic side effect of cisplatin is based on Pt-DNA adduct accumulation in neurons of DRG^[8]. Still, *in vivo* models to prove Pt-DNA adduct-dependent cell damage in DRG neurons are limited, as well as the proof of neuronal cell damage. Here the transmission electron microscope was employed to estimate the potential cellular damage in DRG neurons due to repeated cisplatin exposure. The spinal cord was not screened due to the intact blood-brain barrier that provides natural protection against toxic agents^[10]. The morphological alteration of the nuclear membrane was detected in DRG neurons in cisplatin group (approximately 30% in each animal), with distinct kinking of the membrane (Fig. 3). However, these distinct structural lesions were absent in DRG cells in the other 2 groups.

Fig. 3 Structural alterations in nuclear membrane of DRG neurons. Representative electron transmission scans of DRG neurons from mice treated with cisplatin (A, D), cisplatin plus rhEPO (B, E) or saline (C, F). Mice treated with cisplatin showed morphological changes in the nuclear membrane (arrows in A). Recombinant erythropoietin abolished the damage. No morphological differences in nuclear membrane were found between cisplatin+rhEPO and control groups. Scale bar, 2 μ m. D-F were the magnifications of A-C, respectively. A-C magnification: 3 000 $\times$, D-F magnification: 7 000 $\times$.

4 Discussion

In the present study, we used an animal model to quantify cisplatin-induced visceral neuropathy, and rhEPO was shown to be an attractive compound to counteract cisplatin-

induced visceral neuropathy in mice. Besides, the attenuation of VMR was associated with the lack of structural lesions in the nuclear membrane, and cisplatin-induced visceral neuropathy was accompanied by the damage in neuronal tissue.

It has been revealed that cisplatin primarily targets the DRG cells in the nervous system and loss of function or apoptosis of DRG cells is a hallmark of sensory neuropathy^[18]. Postmortem analysis of neuronal tissues from patients treated with cisplatin revealed high concentrations of platinum in the DRG^[19]. Recently, augmented levels of platination products in the nuclear DNA of DRG neurons have been observed, which confirm the former results^[8]. In a recent study, we showed a significant correlation between the amount of persisting DNA lesions and the degree of cisplatin-induced sensory neuropathy^[10]. Our results support the hypothesis that DNA lesions are a risk factor for impairment of peripheral nerves.

In the present study, the concomitant administration of rhEPO led to significant attenuation of cisplatin-induced VMR enhancement and neuronal tissue damage. The effect of rhEPO on cisplatin-induced neurotoxicity had been demonstrated previously^[20]. Here no difference in sensory nerve conduction velocity was found between control and cisplatin+rhEPO groups. Our previous study has confirmed the neuroprotective effect of rhEPO on drug-induced neuropathy with special emphasis on DNA-adduct formation in DRG neurons, and there is also no difference between control and cisplatin+rhEPO groups^[14]. Apparently, the Pt-DNA adduct accumulation is not affected by rhEPO, thus the neuroprotective property of rhEPO is mediated rather by improved cell survival than by attenuation of Pt-DNA adduct formation. Our observations are in line with the hypothesis that Pt-DNA adducts lead to nuclear damage and consecutively to cell death.

In the peripheral nervous system, erythropoietin and its receptor are expressed in DRG neurons^[11]. Erythropoietin-mediated cytoprotective pathways involve proteins of BCL-2 family, extracellular signal-regulated kinases and phosphatidylinositol 3-kinase/Akt^[21]. In neuronal cells, the nuclear transcription factor NF- κ B is known to be affected by free radicals and cytokines^[22-25]. Binding of erythropoietin to its receptor leads to the activation of the phosphatidylinositol 3-kinase/Akt pathway and NF- κ B pathway. The antiapoptotic proteins including XIAP and C-IAP2 are upregulated subsequently, blocking the activation of specific cell-death

proteases^[26]. More recently, it has been shown that erythropoietin mediates regeneration of adult neurons in the central nervous system via JAK2 and phosphatidylinositol 3-kinase/Akt pathway^[27].

The neurotoxic side effect of cisplatin is still a challenging problem of cancer treatment. Most commonly, a dose reduction or even discontinuation of therapy is required due to the chronic discomfort in patients caused by the neurotoxic side effects. The prevalence of therapy withdrawal ranges between 30%-50%^[28,29]. The sensory neuropathy that causes chronic discomfort in patients remains a challenge for physicians. Recently, we have demonstrated a possible strategy to counteract cisplatin-induced neurotoxicity, with respect to nerve conduction velocity, somatic hypersensitivity and morphological changes in neuronal tissues^[14].

In conclusion, here we present data quantifying cisplatin-induced visceral neuropathy. Besides, rhEPO counteracted cisplatin-induced side effects on the autonomic nervous system. Histopathological examination revealed that the cisplatin-induced damage in the nuclear membrane in DRG could be prevented by co-treatment with rhEPO. These observations are in line with previously published data, which demonstrate that erythropoietin leads to increased cell survival by modulation of anti-apoptotic proteins. Our data suggest an alternative treatment for impaired peripheral nerve function. Further clinical trials in patients suffering from visceral and somatic neuropathy are required to address potential treatment to ameliorate neurotoxic side effects.

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重组人红细胞生成素抑制顺铂引起的内脏痛觉增敏

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摘要: **目的** 顺铂是肿瘤化疗的常用药物, 主要通过损伤细胞 DNA 发挥细胞毒性作用。在肿瘤治疗过程中, 顺铂往往会引起周围神经病变, 进而导致痛觉增敏。本文就重组人红细胞生成素(recombinant human erythropoietin, rhEPO)是否能抑制顺铂引起的内脏痛觉增敏进行研究。**方法** C57BL/6系小鼠经顺铂或顺铂与rhEPO 共同作用8周后, 用肌电检测法观察在结肠直肠扩张性刺激下内脏运动的变化, 并用透射电子显微镜观察背根神经节细胞结构水平的变化。**结果** 顺铂能显著增强结肠直肠扩张性刺激下小鼠的内脏运动反射, 而rhEPO 则能显著减轻这一作用。此外, 透射电子显微镜观察显示rhEPO能显著减轻顺铂引起的背根神经节细胞核膜损伤。**结论** 促红细胞生成素具有神经保护作用。

关键词: 顺铂; 背根神经节; 促红细胞生成素; 内脏神经病变